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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,080	08/20/2003	Evan C. Unger	006086.00019	4717

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BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/644,080	Applicant(s) UNGER ET AL.	
	Examiner Daniel M. Sullivan	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 July 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *105-120*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

DANIEL M. SULLIVAN
PATENT EXAMINER

Daniel M Sullivan, Ph.D.
Primary Examiner
Art Unit: 1636

Continuation of 3. NOTE:

Claims 105, 119 and 120 have been amended to recite that the compound delivered is a therapeutically beneficial compound. As this limitation was not previously presented, the amendment would necessitate reconsideration of the art of record with regard to applicability under 35 U.S.C. §102 and 103 and necessitate a new search. Furthermore, the limitation of the method to delivery of a "therapeutically beneficial compound" raises new issues with regard to therapeutic outcome necessitating further consideration of the claims for compliance with 35 U.S.C. §112.

Continuation of 11. does NOT place the application in condition for allowance because:

Claim Rejections - 35 USC § 112

Claims 119 and 120 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

As stated in the previous Office Action, none of the teachings found in the specification would suggest 500 milliwatts/cm^2 as an upper limit for a range of energy to be used in the method. Thus, the method of claims 19 and 20 wherein the application of ultrasound is limited to the range of 200-500 milliwatts/cm^2 constitutes impermissible new matter.

In response to the rejection of record, Applicant contends that the claimed range is supported because the upper limit of 500 milliwatts per cm^2 recited in claim 119 falls within the range of from about 200 milliwatts per cm^2 to about 10 watts per cm^2 contemplated in the disclosure and, therefore, the range recited in claim 119 is completely within the range recited in the original specification.

This argument has been fully considered but is not deemed persuasive. The courts have determined that a subgeneric range is not necessarily supported by the disclosure of a generic range and a species within the subgenric range. See, e.g., *In re Lukach*, 442 F.2d967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range); *In re Smith*, 458 F.2d 1389,1395, 173 USPQ 679, 683 (CCPA 1972) (a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads). Each case must be decided on its own facts in terms of what is reasonably communicated to those skilled in the art. *In re Wilder*, 736 F.2d 1516, 1520, 222 USPQ 369, 372 (Fed. Cir. 1984).

In the instant case, as pointed out in the previous Office Action, the disclosure as filed does not contemplate a range bounded by an upper limit of 500 milliwatts per cm^2 and there is nothing in the disclosure that would lead one to a range having an upper limit of 500 milliwatts per cm^2.

Applicant is reminded that, According to MPEP §2163, "[t]o comply with the written description requirement of 35 U.S.C. 112, para. 1, or to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. When an explicit limitation

in a claim 'is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation.'" (quoting *Hyatt v. Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998); emphasis added).

For the reasons of record, the skilled artisan at the time the patent application was filed would not have understood that the description requires the range recited in the instant claim 119. Therefore, the range constitutes impermissible new matter.

Claims 105 and 108-120 **stand rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for delivering a nucleic acid into a cell comprising administering a composition comprising a nucleic acid and an organic halide, wherein the composition further comprises a lipid carrier or wherein ultrasound is applied to said cell, does not reasonably provide enablement for the broad scope of a method of delivering any compound into a cell by administration of said compound with any organic halide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In response to the *prima facie* rejection and arguments of record, Applicant first contends that the claims have been narrowed by the recitation of "therapeutically beneficial compound" to a more reasonable breadth. However, as the claim amendments have not been entered, this argument is moot. Applicant's remaining arguments are addressed to the extent that they apply to the claims as they stand at final rejection.

Applicant next points out that it is well known in the art that the delivery of many materials to a cell is often very difficult, particularly if the compound has low aqueous solubility, and one solution to this problem is improve delivery by the application of ultrasound. Applicant contends that combining a compound with a halide and applying ultrasound leads to improved transfection and once this technique is taught with respect to a nucleic acid sequence those skilled in the art would understand that the same general methodology can be easily utilized with respect to other compounds. (P. 13, ¶2.) Applicant contends that because the Examiner concedes that the method is enabled when the compound is a nucleic acid the entire scope of the claims must be enabled. (Bridging pp. 13-14.)

Applicant further contends that because the specification teaches how to practice the method for a nucleic acid, including steps such as mixing the nucleic acid with a halide and applying ultrasound, the specification teaches every relevant detail of the process. Applicant asserts that all that is required to practice the invention with other compounds would be to adjust ratios of the compounds.

Applicant contends that *In re Fisher* requires only reasonable correlation between the disclosure and the scope of the claims, not absolute correlation.

These arguments have been fully considered but are not deemed persuasive. It is acknowledged that *Fisher* requires only reasonable correlation; however, for the reasons set forth in the previous Office Action, the scope actually enabled by the disclosure does not reasonably correlate with the scope of protection sought. Although it is acknowledged that the disclosure is enabling for delivering a nucleic acid into a cell, it must be made clear that, in terms of their chemical properties, all nucleic acids are essentially the same. That is, all nucleic acids are

comprised of the same four nucleoside bases arranged in different order, wherein the sequence of the bases does not materially alter the chemical properties of the compound.

In contrast, genus of molecules such as proteins is made up of species having highly divergent chemical properties, which properties are much different from the chemical properties of the nucleic acids reduced to practice. As pointed out in the previous Office Action (p. 14), the "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The Examiner's position is substantiated by a number of factors evidencing unpredictability in extending the teachings of the specification beyond what is demonstrated in the working examples including the art recognized difficulties encountered in delivering one large class of molecules (i.e., proteins) across plasma membranes (see, e.g., the discussion bridging pp. 7-8 of the previous Office Action); the art recognized unpredictability of structural modifications on delivery molecule function (see, e.g., the discussion of Godbey et al. bridging pp. 7-8 of the Office Action mailed 24 August 2004); the absence of any teaching in the art demonstrating delivery of any compound across a cell wall as contemplated on page 14 of the specification; and the nascent state of the art with regard to microbubble enhanced drug uptake (see, e.g., the discussion bridging pp. 8-9 of the previous Office Action).

Given the nascent state of the relevant art and the tremendous breadth of the claims, the skilled artisan seeking to practice the instant claimed method according to its full scope would be forced to identify which of the many thousands of combinations of organic halide and compound encompassed by the claims would be operative in a method of introducing a compound into a cell and determine how to apply ultrasound sufficient to induce uptake of any compound into any cell. By way of guidance in determining the operative embodiments of the invention, the specification provides only suggestions of preferred embodiments of the organic halide and very limited working examples, which provide the method practiced with a single compound (*i.e.*, DNA) and five species of organic halide, wherein the composition further comprises additional ingredients (*i.e.*, transfection reagents) that would provide delivery of a nucleic acid into a cell even in the absence of the organic halide. Given these teachings the skilled artisan would have no idea which embodiments of the claimed invention would be operative, beyond those wherein the compound is a nucleic acid and the method further comprises a lipid carrier or application of ultrasound. Thus, operability of each of the many thousands of combinations encompassed by the claims would have to be determined independently by empirical experimentation.

Contrary to Applicant's assertion, a teaching that the compound to be delivered should be mixed with a halide does not enable the broad scope of what is claimed. Rather, what is required is a teaching of which compound mixed with which organic halide provides a composition capable of delivery into any cell, including which organic halides can be used in conjunction with ultrasound to deliver a compound across a cell wall. Applicant's contention that practicing the invention with respect to compounds other than nucleic acids would require only adjustments with respect to the ratios of the compounds and with respect to the protocol of applying

ultrasound is simply not consistent with the broad scope of the claims, the chemically heterogeneous nature of compounds to be delivered and the unpredictable nature of the art.

Finally, Applicant cites *In re Wands* and contends that a reasonable quantity of experimentation is allowed if it is routine or if the specification provides enough guidance. However, with regard to the legal standard for "undue experimentation", *In re Wands* is clear, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* ...They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims" (8 USPQ2d 1400, page 1404). The present arguments appear to be Applicant's opinion of what is routine experimentation and not the legal analysis set forth in *In re Wands*. In contrast, analysis of the instant claims according to the "Forman factors" is clearly set forth in the previous Office Actions.

It is further noted that the facts in *Wands*, particularly the scope of what is claimed and the level of predictability in the art, are quite different from the facts in the instant case. The claims in *Wands* were limited to a product consisting of a single class of antibody capable of detecting a single antigen, as opposed to the broad scope of the method presently claimed, and the Court in *Wands* reasoned as follows (1406-1407; emphasis added):

> When Wands' data is interpreted in a reasonable manner, analysis considering the factors enumerated in *Ex parte Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the

> art at the time when the application was filed, and all of the methods needed to practice the invention were well known. The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations. Reasonably interpreted, Wands' record indicates that, in the production of high-affinity IgM antibodies against HBsAG, the amount of effort needed to obtain such antibodies is not excessive. Wands' evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure.

In contrast to the facts in Wands, the instant claims are tremendously broad, delivering chemically disparate compounds into cells is not routine and the working examples are far from representative of the vast majority of embodiments within the scope of the claims.

Thus, in view of the record as a whole, it is clear that practicing the invention commensurate with the full scope of what is claimed would require undue experimentation. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 103

Claims 19 and 20 **stand rejected** under 35 U.S.C. 103(a) as being unpatentable over Unger (WO 94/28780; made of record in the previous Office Action).

In response to the *prima facie* rejection of record, Applicant contends that Unger does not render obvious the claimed invention because Unger provides no motivation or suggestion to the

energy flux of 200-500 mW per cm^2. Applicant contends that the Examiner has provided no justification why one skilled in the art will be motivated to modify Unger to arrive at what is claimed. Applicant contends that a showing that the proposed modification is desirable is required.

These arguments have been fully considered but are not deemed persuasive. As described in the previous Office Action, the instant application teaches that the range recited in the claim falls within a range typical of therapeutic ultrasound (p. 49, ¶2). Unger *et al.* teaches, "Higher energy ultrasound such as commonly employed in therapeutic ultrasound equipment is preferred for activation of the therapeutic containing gaseous precursor-filled liposomes" (p. 56, ll. 16-19; emphasis added). Thus Unger et al. also provides a generic teaching that the ultrasound energy in the range commonly employed in therapeutic applications is desirable for use in the method. Therefore, the only distinction between what is claimed and what is taught in the prior art is the recitation in the claim of what appears to be an optimum range, which difference does not support patentability of subject matter claimed.

Contrary to Applicant's characterization, the Examiner does provide substantial legal basis for concluding that a claim that differs from the prior art only insofar as it recites a range falling within a generic teaching found in the art is *prima faice* obvious. The Examiner cites, *inter alia*, *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), which states, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation" and *In re Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382, which states, "The normal desire of scientists or artisans to

improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."

Thus, contrary to Applicant's assertions, the Examiner has not resorted to speculation, unfounded assumptions or hindsight reconstruction. Instead, the *prima facie* rejection provides a reasoned analysis based upon the facts in the instant case and relevant legal precedent.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §103(a) as obvious over the art.